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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

Radiographic Progression in Ankylosing Spondylitis: From Prognostication to Disease Modification

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Abstract

Purpose of Review Pain, functional limitation, and spinal damage are the three main domains that have significant impact on various aspects of axial spondyloarthritis (axSpA).

Recent Findings Several randomized controlled trials (RCTs) showed a beneficial effect of non-steroid ant-inflammatory drugs (NSAIDs) and biologic treatments on pain and function. The effect of available treatments on spinal damage is still of interest and is being studied.

Summary In this article, we review the literature on radiographic progression in axSpA. We discuss the natural course of spinal progression, predictors of spinal damage, and the effect of lifestyle changes and medications on radiographic progression in axSpA.

Keywords Spondylarthropathies · Ankylosing spondylitis · Disease progression · Outcomes assessment · Tumor necrosis factor-alpha · Non-steroidal anti-inflammatory agents · Smoking · Diagnostic imaging

Introduction

The axial spondyloarthritis (axSpA) concept covers a broad spectrum of patients with inflammatory disease of the spine. In the ASAS (Assessment of SpondyloArthritis international Society) classification of axSpA, this group comprised two categories: (i) patients with radiographic sacroiliitis as defined by the modified New York criteria (mNYc) [1] and (ii) patients without diagnostic radiographic changes in the sacroiliac joints (SIJ), in which case the term non-radiographic axial SpA (nr-axSpA) is used [2]. Ankylosing spondylitis (AS) is the prototypical SpA disease where inflammatory activity leads to significant changes in the spine that are detectable on X-rays. Pain and functional limitation are one of the earliest findings of the disease. On the other hand, in the long term, new bone formation (syndesmophytes/bridging syndesmophytes) may accompany the clinical picture.

AS is a slowly progressing disease, and assessment of structural changes longitudinally with long-term follow-up is required to study spinal progression. Moreover, several factors may play a role in spinal fusion. Recognizing these factors, understanding their role as well as strength of association and controlling for them are required to fully understand the process of spinal fusion [3]. The concept of disease modification ties closely into this concept, and studying the effect of drugs on syndesmophyte formation is not trivial. Short of having a large cohort of patients who have been followed for 6–8 years of follow-up, a reasonable approach to study disease modification may be using contemporaneous controls that are well matched on the identified predictors. Furthermore, studying AS patients at higher risk for progression may decrease the need for larger cohorts and longer-term follow-up.

Currently, conventional radiography is the gold standard for assessment of the extent and severity of spinal disease caused by axSpA [4]. For quantification of spinal damage, several scoring systems have been developed.

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Among them, the Bath AS Radiology Index (BASRI) [5], the Stoke AS Spine Score (SASSS) [6], and the modified SASSS (mSASSS) [7] are the most widely used ones. In recent years, mSASSS has become the preferred method to score spinal damage in axSpA as it has been shown to be superior in terms of reliability and sensitivity to change [8, 9]. Additionally, ASAS and OMERACT (Outcome Measures in Rheumatology) groups endorsed the usage of mSASSS in clinical trials which also contributed to its widespread usage [10]. In mSASSS, the total score ranges from 0 to 72, reflecting structural changes including squaring, sclerosis, erosion, syndesmophyte, and bridging syndesmophyte formations [7]. For scoring, a lateral view of anterior vertebral corners (VCs) of cervical (lower border of C2 to upper border of T1) and lumbar (lower border of T12 to upper border of S1) spines is used [7].

Based on clinical data and experts' opinion, a minimum interval of 2 years between X-rays is recommended to detect any significant change [5, 11, 12]. On the other hand, there is currently no established cut-off for defining progression. Based on the longitudinal cohort studies, a change of two mSASSS units in 2 years (rate ≥ 1 unit/year) or development of a new syndesmophyte is considered as progression in AS [13–15]. Some researchers suggested additional classification to identify the rate of progression: (1) slow, < 2.0 mSASSS units or not more than one syndesmophyte within 2 years, (2) moderate, 2.0–5.0 mSASSS units or not more than two syndesmophytes within 2 years, and (3) fast, > 5.0 mSASSS units or more than two syndesmophytes within 2 years [16, 17].

The Natural Course of Radiographic Progression

Several studies attempted to identify progression rates and its predictors. Baraliakos et al. studied 146 TNF-naive AS patients and showed that 45.2% of the group had progression (equivalent to at least one syndesmophyte) within 2 years [16, 17]. The mean disease duration of the group was 23.6 years (11.2), and 63.7% of the patients had at least one syndesmophyte [16, 17]. The only predictor for future progression was the number of baseline syndesmophytes [16]. Further subgroup analysis showed that overall progression rates were similar between men and women [17]. However, there was a trend regarding higher progression in the cervical spine in women and in the lumbar spine in men [17]. Another study concerning 210 early axSpA patients (disease duration ≤ 10 years) in the German Spondyloarthritis Inception cohort (GESPIC) showed that 14.3% of the total group (20% AS and 7.4% non-radiographic axSpA [nr-axSpA]) showed radiographic progression after 2 years [14]. Overall, 30.4% of the AS and 13.7% of the nr-axSpA patients had baseline damage as assessed by syndesmophytes. After 2 years, new syndesmophytes developed in 11.3% and 3.2% of the patients with AS and nr-axSpA, respectively. A subgroup analysis of this cohort showed similar progression rates between patients with a disease duration of ≤ 5 vs. > 5 years. However, authors noted a higher mSASSS change (although not statistically significant) in AS patients with a symptom duration of > 5 years suggesting a "window of opportunity" early in the disease course [14]. The presence of radiographic damage at baseline, increased acute phase reactants, and smoking were identified as independent predictors of spinal progression in this group [14]. In a study concerning 132 AS patients in the OASIS (Outcome in AS International Study) cohort, new syndesmophytes developed in 33% and 48% patients within 2 and 4 years, respectively. The mean disease duration of the group was 11.7 years (9.3), and 61% of the patients had at least one syndesmophyte at baseline [18]. Here too, in multivariable regression analysis, only the presence of existing syndesmophytes was a significant predictor of progression. When existing syndesmophytes were taken out from the model, older age and male gender were the significant predictors of progression [18]. In a further study with larger numbers of patients ($n = 186$), there was a 22% progression rate (based on mSASSS ≥ 2) in the first 2 years (46% when taken into account all 2-year intervals in the 12 years) [15]. On the other hand, approximately 30% of the patients had at least one syndesmophyte development in the first 2 years. Progression in the cervical spine was significantly higher than in the lumbar region. Radiographic progression occurred significantly faster in men than in women, in HLA-B27-positive than in HLA-B27-negative patients, and in patients with a baseline mSASSS ≥ 10 (which was the median value) compared with those with a baseline mSASSS < 10 [15]. Table 1 summarizes the progression rates and predictors of progression in longitudinal studies.

In summary, both AS and nr-axSpA patients progress over time with less likelihood of progression in nr-axSpA. Rates of progression can vary between 20 and 45% at 2 years in AS, and it is expected to have more progressing patients in longer follow-ups. Several predictors have been linked with further structural changes including higher inflammatory burden, male sex, positivity for HLA-B27, smoking, and presence of baseline damage, with the latter one seeming to be the common denominator in all studies. In patients with shorter disease duration (≤ 5 years), there may be a "window of opportunity" as there is less progression compared to the later stages. It is still unclear if the bone formation pathways are triggered after an initial lag phase during which inflammation predominates.

Table 1 Summary of the longitudinal studies regarding rates and predictors of progression in axSpA

Reference	Disease type	Number	Age	Baseline mSASSS	mSASSS change	Rate of progression at 2 years	Predictors of progression
[16, 17]	AS	146	54.2 (12.3)	20.5 (14.4)	1.3 (2.5)/year	45.2%	Number of baseline syndesmophytes
[14]	axSpA	210	37.1 (10.6)	4.25 (8.3)	0.73 (2.3)/2 years	14.3%	Presence of baseline syndesmophytes, high baseline ESR or CRP, and current smoking
	AS	115	36.8 (11)	5.9 (10.3)	0.95 (2.8)/2 years	20%	
	nr-axSpA	95	38.7 (9.9)	2.3 (4.2)	0.46 (1.6)/2 years	7.4%	
[18]	AS	132	44.4 (12.1)	12.8 (17.5)	2.5 (4.2)/2 years	33%	Presence of baseline syndesmophytes, male sex, and age
[15]	AS	186	43 (12)	11.6 (16.2)	2 (3.5)/2 years	22%	Men, HLA-B27 positive and mSASSS ≥ 10

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *nr-axSpA* non-radiographic axial spondyloarthritis

Effect of Treatments and Lifestyle Changes on Radiographic Progression

Anti-TNF Treatments

The discovery of the tumor necrosis factor (TNF) alpha-targeting medications revolutionized the treatment of axSpA. It has been reported that nearly 60% of the active axSpA patients can achieve ASAS20 clinical response in 3–12 months of follow-up [27]. Currently, there are five molecules available in the market for the treatment of axSpA including infliximab (INF), etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP). In recent years, we have seen a number of studies addressing the effect of TNFi on imaging findings. Some focused on signs of active inflammation on MRI while others investigated the effect of TNFi treatments on structural changes as seen in conventional x-rays (Table 2).

MRI Studies Investigating the Effect of TNFi on Spinal Changes

MRI-related studies regarding regression of inflammation in spine and sacroiliac joints (SIJs) are available for all TNFi treatments. In this respect, several scoring methods (ASspiMRI, SPARCC) have been used and some studies also focused on structural changes, which were mainly evaluated from T1 sequences. Studies in active AS nr-axSpA patients are available [28]. Nearly all studies showed a clear-cut benefit of TNFi in decreasing inflammation compared to placebo. Some studies provided long-term results showing maintenance of the initial good response up to 3–4 years [29, 30].

In an earlier study, 20 active AS patients were randomized to INF or placebo [31]. At 3 months, there was a significant reduction in inflammatory spinal lesions in the active treatment group (48% vs. 9.2%). A two-year follow-up of these patients showed an overall 69.7% improvement in spinal inflammatory lesions compared to baseline assessment. On the other hand, spinal structural changes continued to progress (20.7% higher compared to baseline) [31]. In another placebo-controlled study, at week 12, low-dose (3 mg/kg) INF treatment ($n = 18$) resulted in a 57.2% decrease in inflammatory lesions compared to 3.4% reduction in the placebo ($n = 18$) group [32]. ETN and its effect on spinal and SIJ lesions have also been extensively studied. In an RCT, active AS patients assigned to ETN ($n = 19$) and placebo ($n = 21$) arms were evaluated in terms of spinal inflammatory and chronic changes. At week 24, inflammatory lesions improved by 72.8% and 4.3% for ETN and placebo patients, respectively. On the other hand, when compared to baseline scores, both groups had an increase in chronic changes by 6.1% (ETN) and 13.3% (placebo) [19]. Similar observations have also been reported with ADA. In this respect, Lambert et al. reported a 53.6% reduction in spine lesions with ADA ($n = 38$) compared with a 9.4% increase in inflammation scores in placebo ($n = 44$) treated patients at week 12 [33]. Meanwhile, the reduction in the SIJ score was 52.9% in ADA-treated AS patients vs. 12.7% in the placebo group [33].

As mentioned earlier, the beneficial effect of TNFi regarding suppression of inflammation is not limited to AS. In a study concerning early active IBP patients, the study group was randomized to placebo ($n = 20$) and INF ($n = 14$) treatments and assessed at week 16 [34]. At baseline, all subjects had active SIJ lesions and these were completely resolved by 77.3% and 22.2% in the INF and placebo groups, respectively [34]. In the EMBARK study, nr-axSpA patients who received ETN ($n = 106$) had significantly greater reductions from baseline to week 12 compared with placebo-treated patients ($n = 109$) in both the SIJ (46.9% vs. 10.9%) and spinal inflammation (45.4% vs. 33.4%) scores [28].

Aside from short-term improvement, several long-term studies have also been published. In the GO-RAISE study, researchers investigated the effect of GOL (both 50 mg

Table 2 Some studies investigating radiographic changes in biologics and conventionally treated patients

Reference		Number	Follow-up	Disease duration (year)	Baseline mSASSS	Change in mSASSS/ 2 years	Comments
[19]	INF	41	2	15.5	12.1 (16.9)	0.4 (2.7)	NS change, used historical cohort for comparison
	Controls	41		5.5	5.9 (13.4)	0.7 (2.8)	
[20]	INF	201	2	10.2	17.7 (17.9)	0.9 (2.6)	NS change, used historical cohort for comparison
	Controls	192		11.3	15.8 (18.1)	1 (3.2)	
[21]	ETN	257	2	10	16 (18.3)	0.91 (2.45)	NS change, used historical cohort for comparison
	Controls	175		11	14 (17.6)	0.95 (3.18)	
[22]	ADA	307	2	11.2	19.8 (19.3)	0.8 (2.6)	NS change, used historical cohort for comparison
	Controls	169		11.3	15.8 (17.6)	0.9 (3.3)	
[23]	GOL 50 mg	111	4	11*	11.7 (16.4)	0.8	NS change between two dose groups
	GOL 100 mg	122		11*	13.5 (18.9)	1	
[24]	INF	22	8	15.8	13.2 (17.6)	1.8	NS between the groups but significantly less progression in the INF group after correcting to baseline damage
	Controls	34		20.7	14.2 (13.8)	3	
[25]	TNFi	269	5	11.3	18.9 (18)	2.4	NS change
	Controls	341		8	15.7 (15.5)	1.8	
[26]	SEC 75	82	2	7.8	10.8 (16.7)	0.31 (3.04)	NS change between dose groups
	SEC 150	86		6.6	9.6 (16.6)	0.30 (1.94)	

All continuous data represents mean values instead * which indicates the median. Standard deviation of mean values is given in parentheses

ADA adalimumab, *ETN* etanercept, *GOL* golimumab, *INF* infliximab, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score, *NS* non-significant change, *SEC* secukinumab, *TNFi* tumor necrosis factor inhibitory

and 100 mg) in active AS [35]. At week 14, placebo treatment ($n = 23$) showed 20% improvement in spinal inflammation while there was a 56.5% and 52% reduction with the doses of 50 mg ($n = 37$) and 100 mg ($n = 38$), respectively. The improvement was maintained at week 104 at a rate of approximately 60% [35]. A subgroup analysis of the ESTHER trial showed that axSpA patients receiving ETN for 3 years had a complete resolution of osteitis at rates of 38.9% and 50% in SIJs and spine, respectively [29]. Another long-term study from the RAPID-axSpA cohort has recently been published [30]. After a 4-year treatment with CZP, spinal inflammatory lesions reduced by 65.4% and 57.3% compared to baseline values in both nr-axSpA ($n = 65$) and AS ($n = 92$) patients, respectively. Similar reductions were also observed for SIJ inflammation in both groups (69.6% vs. 66.7%) [30].

The question regarding the resolution of inflammation and its impact on further structural changes (such as syndesmophytes) has been investigated extensively. A prospective follow-up study of 41 AS patients receiving anti-TNF or standard therapy showed that new syndesmophytes at the 2-year follow-up developed significantly more frequently in VCs with inflammation (14.3%) than in those without inflammation (2.9%) [36]. Some suggested that new syndesmophytes paradoxically developed more frequently from VCs where corner inflammatory lesions (CILs) had completely resolved with TNFi on follow-up MRI (42.9%) as compared to VCs where no CIL was demonstrable on either baseline or follow-up MRI (2.4%) [37]. In another study, a follow-up of 73 AS patients who were treated with INF over 5 years was analyzed. According to the results, VCs with both inflammation and fat deposition at baseline had the highest risk for developing syndesmophytes with a relative risk of 3.3. On the other hand, the majority (57.4%) of new syndesmophytes developed in VCs that had neither inflammatory nor fatty lesions on the baseline MRI which was another important finding of the study [38]. Machado et al. reported that presence of CIL and fat deposition demonstrated a higher risk of further syndesmophyte formation with adjusted ORs of 1.75 to 1.98 and 1.60 to 2.32, respectively, at any time point [39]. The combination of CIL and fatty changes at the same VC increased the strength of the association (adjusted OR 2.12 to 2.73). However, 40–66% of new bone still developed in VCs without CIL or fat deposition [39].

In summary, TNFi treatments have significant impact on suppressing inflammatory spinal lesions in both AS and nr-axSpA patients. According to the results, this seems to be a class effect as all available molecules have shown to decrease the inflammation-related changes. Even though studies link inflammation at VCs to the development of syndesmophyte at the same level, VCs without any evidence of inflammation (either spontaneous or obtained by treatment) still confer a significant risk of syndesmophyte development. This may be the consequence of ongoing inflammatory activity at histopathological level that is not evident by MRI or because MRI changes are dynamic and may turn positive at a future date [36].

X-Ray Studies Investigating the Effect of TNFi on Spinal Changes

The relationship between anti-TNF treatments and its effect on structural changes has been of interest for several years. As these treatments have significant impact on disease activity and thus on clinical symptoms, there is an expectation of halting/slowing the progression and maintaining physical function. Several RCT-derived extension studies and longitudinal observational cohort analyses have been published on this topic [13, 19–25]. Some of the studies suggested decreased radiographic progression in TNFi-treated patients. In the first multicenter study, there were 334 AS patients of whom 201 have been treated with TNFi [13]. The mean disease duration for each treatment group was 16 years, and the mean biologic duration was 2.5 years. In this study, TNFi treatment was associated with a 50% reduction in the odds of progression. Researchers also reported a higher progression rate in patients who delay starting TNFi by more than 10 years compared to those who started earlier [13]. In another study, 432 AS patients with up to 10 years of follow-up were analyzed [40]. Patients who received continuous TNFi at least 2 years prior to their baseline x-rays showed 50% less radiographic progression during the next 2-year interval compared to non-TNFi-exposed patients [40]. Importantly, achieving an inactive disease state (ASDAS ≤ 1.3) with TNFi resulted in significant reduction in radiographic progression [40]. In a Dutch study, 210 AS patients with a median disease duration of 14 years were retrospectively analyzed [41]. All patients received TNFi, and data was available up to 8 years of follow-up. According to the results, there was a linear course with stable progression rates in patients with 4 years of follow-up. Beyond that period, there was a nonlinear course with reducing progression suggesting a beneficial effect in reducing progression with long-term TNFi use [41].

In a recent study, axSpA patients receiving CZP treatment for 4 years were investigated [30]. In patients with AS, the mean mSASSS change between baseline and week 204 was 0.98 units. This was calculated as 0.06 in patients with nr-axSpA. The overall progression was less in years 2–4 compared to the first 2 years [30]. A beneficial effect with the use of TNFi was proposed considering the drop-in progression after the first 2 years. It appears that 2–4 years is the minimum period of TNFi use for us to see the benefits on disease modification and delay in starting treatment may increase the likelihood of progression. Some studies with historic controls did not show a significant effect of TNFi on spinal progression [19–22, 24, 25]. However, despite these negative results, it should be noted that the observation time was limited to 2 years [19–22].

Other Biologics

Recently, the IL-17 pathway has been recognized as an important player in the pathogenesis of axSpA. The anti-IL-17 inhibitor secukinumab (SEC) is approved for use in AS patients and is as efficacious as TNFi [27]. The interesting question is whether treatments targeting IL-17 have a similar effect on radiographic progression. In a recent study, Braun et al. published the 2-year results of SEC on clinical and radiographic outcomes [26]. In this study, AS patients were randomized to two dose groups of SEC (75 mg, $n = 82$, and 150 mg, $n = 86$). Patients in the placebo group switched to one of the dose groups at weeks 16 or 24. Nearly 60% of the cohort had syndesmophytes and increased CRP at baseline. The mean change in mSASSS over 104 weeks was 0.30 (2.53) in the total group and was similar in between the dose groups. As expected, progression was higher in patients with baseline damage and high CRP [26]. The 4-year results of this study were published as an abstract and showed a numerically lower progression in the 150-mg dose compared to the 75-mg dose, but this was statistically not significant [42]. Compared to biologically naïve patients enrolled in the ENRADAS study and receiving diclofenac over 2 years, there was no significant difference in radiographic progression in patients from the measure 1 study receiving secukinumab [43]. Thus, no definitive answer on the disease-modifying effect of secukinumab is available as yet. A study currently underway may yield some interesting results. A phase 3, 104-week randomized study of secukinumab and GP2017 (adalimumab biosimilar) to demonstrate reduction of spinal progression is currently recruiting [44].

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment option for patients with axSpA [45]. NSAIDs improve clinical symptoms including spinal pain and morning stiffness. They also positively affect physical function [46, 47]. Some patients may benefit from moderate doses while others require maximum tolerated doses. Similarly, some patients require only on-demand usage while others may need continuous and long-term use of NSAIDs [47]. The disease-modifying potential of NSAIDs has been investigated in some studies [48]. The earliest report on this topic is a retrospective study conducted by Boersma et al. which included 40 AS patients [49]. Three groups (continuous, irregular, and without treatment) were assessed, and there was reduced spinal ossification in long-term and regular use of phenylbutazone in patients [49]. In a controlled trial, AS patients were randomized to continuous ($n = 76$) or on-demand ($n = 74$) celecoxib therapy. At baseline, both dose groups had similar mSASSS units, and after 2 years, mean progression amount was significantly higher in the on-demand users (1.5 ± 2.5 vs. 0.4 ± 1.7 units

respectively). The number of progressing patients was also significantly higher in the on-demand group according to mSASSS > 0 (45% vs. 22%) and ≥ 3 (23% vs. 11%) cut-off values [50]. A post hoc subgroup analysis of this study revealed that the effect of slowing radiological progression with continuous NSAID therapy was more pronounced in patients with elevated C-reactive protein (CRP) [51]. A retrospective analysis of the German Spondyloarthritis Inception Cohort (GESPIC; $n = 164$; 88 with AS and 76 with nr-axSpA) investigated patients' NSAID intake using an NSAID score [52]. There was significant and less spinal progression in AS patients with high NSAID intake (a score of ≥ 50) compared with low NSAID intake. However, this effect was only relevant for patients with baseline damage (in terms of syndesmophytes) and with elevated CRP. On the other hand, there was no difference between low and high NSAID intake patients in the nr-axSpA group over a 2-year period [52]. The ENRADAS study referred to earlier is a recent RCT. Sieper et al. investigated the effect of continuous ($n = 85$) vs. on-demand ($n = 82$) diclofenac (150 mg) usage on radiographic progression over 2 years in AS patients [53]. In contrast with the previous studies, there was a non-significant but higher mean progression observed in the continuous therapy group compared to on-demand users (mean mSASSS change over 2 years was 1.28 vs. 0.79 units, respectively). Furthermore, subgroup analysis regarding patients with high vs. low NSAID intake and patients with high vs. low CRP values did not disclose any difference between the treatment arms. In summary, the net effect of NSAIDs in slowing radiographic progression is still in debate. Available data suggests some effect in continuous NSAID users, particularly in patients with higher inflammation levels. However, when considering potential adverse events related with NSAID usage, available evidence is not adequate to recommend continuous use of NSAIDs in AS patients who are otherwise well controlled for the sole purpose of preventing radiographic progression. Many other factors including age, GI tolerance, concomitant IBD, cardiovascular risk, NSAID response, and whether patients are well controlled with or without a biologic response modifier have to be considered.

Other Pharmacological and Non-pharmacological Treatments

Sulfasalazine (SSZ) is the most studied conventional oral drug in the treatment of axSpA. However, its beneficial effect is limited to patients with peripheral joint involvement and current evidence does not support additional therapeutic benefit in the patients with predominant axial manifestations [45]. There is limited data regarding SSZ and its effect on radiographic progression. In an RCT of SSZ ($n = 20$) and placebo ($n = 20$), Taylor et al. assessed changes in lumbar spine and showed that both placebo and SSZ groups had progressed by similar amounts within 12 months of follow-up [54]. However, small sample size and shorter follow-up period of this study were the main limiting factors. It is well-known that patients with axSpA benefit from non-pharmacological treatment, and they complement pharmacological therapy. However, data on the impact of physiotherapy on radiographic progression is scarce. This is mostly because of confounding effects of medical treatment and difficulty quantifying physical activity. Thus, further studies are needed to determine the effect of non-pharmacological treatments on radiographic progression.

Smoking

It has been reported that smoking has a poor impact on the outcome of axSpA. Several cross-sectional and retrospective cohort studies analyzed the effect of smoking on different aspects of axSpA. The strong effect of smoking on disease progression as well as the impact of the amount of smoking as quantitated by pack years was reported in a multicenter study [13]. A subgroup analysis of the DESIR cohort suggested that smokers ($n = 123$) had an earlier onset of back pain, higher disease activity scores, worse functional status, higher inflammation on sacroiliac joints and spine, and higher structural damage compared to non-smokers ($n = 174$). In another study, Ramiro et al. analyzed the effect of smoking on disease in patients from the OASIS cohort. For every one unit, ASDAS increase smokers ($n = 49$) had more radiographic progression compared to non-smokers ($n = 78$) [55]. In patients with early axial SpA from the GESPIC cohort ($n = 210$), smoking status was independently associated with higher progression rates [14]. A recent report from the Scottish SpA Registry suggested that patients who exposed smoking ($n = 562$) had significantly poorer disease activity, function, and metrology compared to non-smokers ($n = 384$) [56]. Furthermore, compared to current smokers, ex-smokers reported less disease activity and significantly better quality of life [56]. In a prospective longitudinal study of 212 AS patients, current smoking was strongly associated with the rate of progression of functional disability [57]. A subgroup analysis of the Swiss Registry Study on axSpA patients receiving TNFi showed that the odds for reaching a 50% improvement in BASDAI response or the ASAS criteria for 40% improvement after 1 year of treatment was significantly lower in current smokers than in non-smokers [58]. Taken together, smoking interacts with many aspects of axSpA and could negatively affect patient outcome by limiting function, increasing disease activity, decreasing the effectiveness of anti-TNF treatment, and stimulating structural damage [59, 60]. Therefore, quitting smoking is one of the essential steps in disease modification of axSpA.

High Disease Activity

As mentioned earlier, radiographic progression is one of the main mediators of decreased function and disability. Some of the cohort studies investigated the effect of high disease activity on radiographic progression. Ramiro et al. used several disease activity measures including ESR, CRP, BASDAI, and ASDAS to predict their effect on progression [61]. According to the results, all disease activity measures were longitudinally associated with radiographic progression in AS. Patients with a very high disease activity state (ASDAS > 3.5) had an additional progression of 2.31 mSASSS units/2 years compared with inactive (ASDAS < 1.3) patients. The effect of disease activity on radiographic damage was more profound in men than in women, and was stronger in the shorter disease duration group [61]. In a further study, early axSpA patients have been investigated [62]. There was a clear increase in radiographic spinal progression with increasing disease activity assessed by time-averaged ASDAS. Patients with very high disease activity had a remarkably high radiographic spinal progression rate in comparison to patients with lower disease activity. This relationship between ASDAS and radiographic spinal progression was similar for both nr-axSpA and AS [62]. In summary, higher disease activity results in

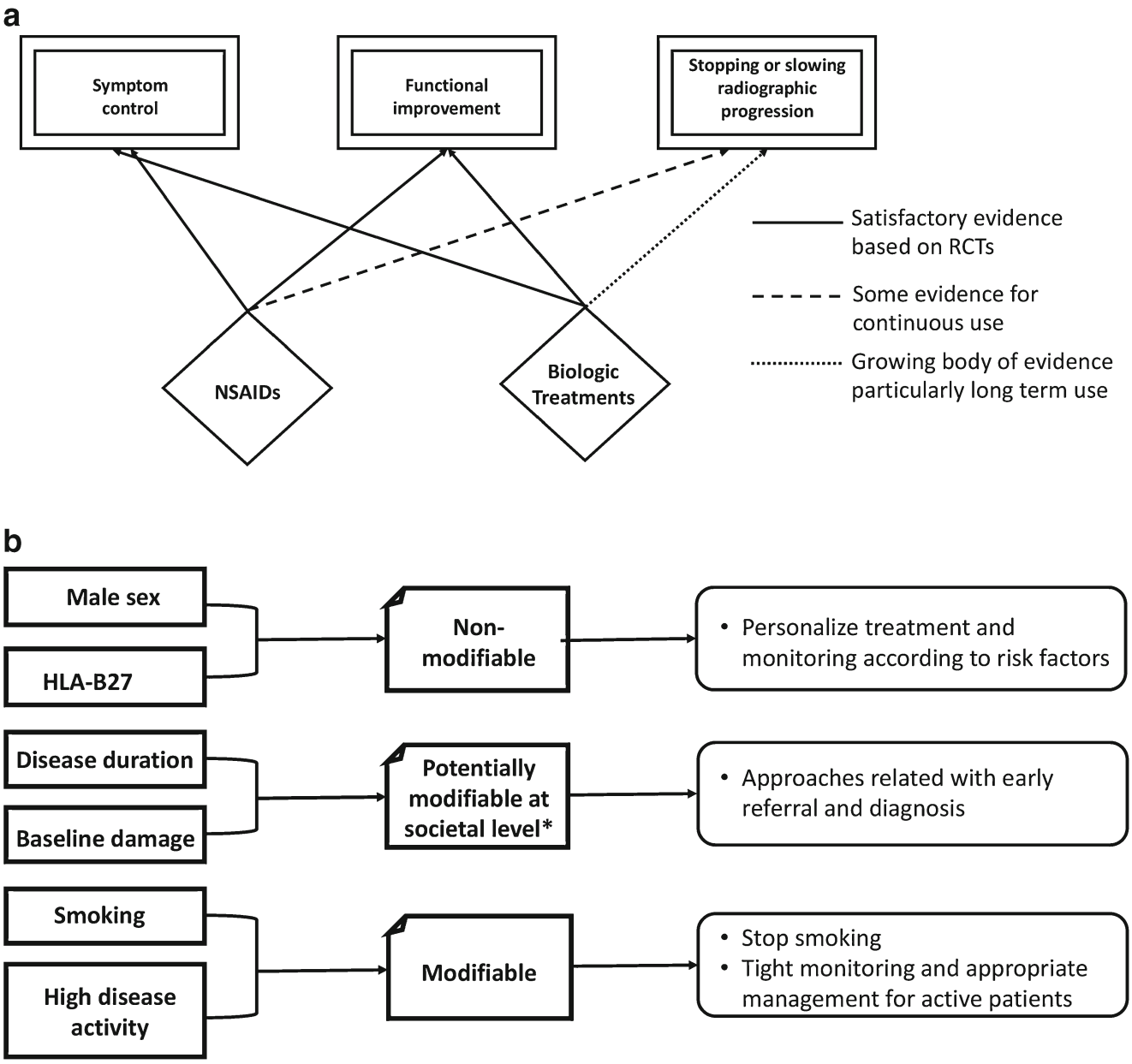

Fig. 1 Disease modification, treatment, and risk factors for progression. **a** The fundamental principles of the axSpA treatment based on evidence-based data. **b** Summary of the follow-up strategy for axSpA patients according to the established risk factors of radiographic progression. *The disease duration and baseline damage has already happened at the presentation. NSAIDs, non-steroidal anti-inflammatory drugs; RCTs, randomized controlled trials.

radiographic progression in both early and longstanding axSpA patients, which serves a reasonable target for disease modification.

Functional Impairment and Its Link With Radiographic Changes

Pain and stiffness due to disease activity and structural damage are considered to be the main underlying causes for physical function impairment in axSpA. However, there are limited studies addressing the influence of radiographic spinal damage on physical function. In a longitudinal study, including 217 AS patients, baseline and 2-year follow-up data was investigated to study the effect of radiographic damage on functional status. In this cohort, there was moderate-good correlation between function (determined by BASFI and DFI) and mSASSS. They also noted a significant worsening of BASFI in patients who have > 36 mSASSS units, which could possibly be considered as a cut-off value for this association. On the other hand, they showed that functional impairment was independently predicted by both disease activity (BASDAI) and mSASSS [63]. In another longitudinal study, 210 patients with early axSpA who completed a 2-year clinical and radiographic follow-up were investigated [64]. They replicated the association of structural damage, function, and disease activity in a group of shorter disease duration axSpA patients. Given a higher association of BASDAI on BASFI compared to mSASSS, authors suggested that in the early stages of axSpA, disease activity impacts function more while structural changes may become more important in the later periods [64]. Another study analyzed the effect of long-term (10 years) TNFi treatment on functional status in AS [65]. All patients ($n = 60$) were on biologic therapy, and after the induction period (12 weeks), BASFI remained stable despite the advance in radiographic changes. Despite the small number and absence of a control group (e.g., patients not using TNFi), their findings indicate that tight control of inflammation may counterbalance the negative effect of structural damage on function in AS [65].

In summary, radiographic damage is a well-known negative predictor of functional status in axSpA. Spinal changes may have more impact on function in the later stages of the disease. Unlike the radiographic damage, disease activity effects the entire disease course and could be reversed with appropriate treatment. Therefore, tight control of disease activity is one of the essential steps in maintaining function through symptom control and halting or slowing radiographic damage.

Conclusion

Disease modification in axSpA involves prevention of structural changes in the spine and is closely linked to symptom control and functional improvement (Fig. 1). Biologic medications have the best evidence for disease-modifying properties. Lifestyle changes such as quitting smoking should be considered as an adjunctive approach in both early- and advanced disease-stage groups. Risk stratification based on available data could be helpful in identifying patients with high risk for progression. In such cases, tight monitoring and early commencement of biologics could potentially have an impact on slowing or preventing structural changes. To identify patients in the early disease stage, creating awareness of axSpA is essential. There is also a need for effective and early referral strategies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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